

AMENDMENT AND RESPONSE TO OFFICE ACTION

Remarks

Amendment to the Claims

Claim 55 has been amended to specify that the implant contains a plurality of particles having a diameter ranging from 10 nanometers to 10 microns, and that the particles contain one or more cytokines. Claim 1 has also been amended to remove reference to one or more factors. Support for the amendments to claim 55 can be found in the specification at least at page 12, para. 4 and page 24, para. 3.

New claims 68 -70, which depend from claim 55, have been added. New claim 68 specifies that the implant further comprises one or more factors selected from the group consisting of growth factors, angiogenic/vasculogenic factors and bone marrow recruiting factors. New claim 69 specifies particular angiogenic/vasculogenic factors that can be found in the implant. Support for new claims 68 and 69 can be found in the specification at least in original claim 21. New claim 71 specifies that the particles contain one or more biodegradable polymers. Support for this amendment can be found in the specification at least at page 13, para. 2 and 4.

New claims 71-74 have been added. New independent claim 71 defines a plurality of particles for recruiting progenitor cells to a site in the body of a subject. Support for claim 71 can be found in the specification at least at page 12, para. 4, page 13, para. 3 and page 24, para. 3. New claims 72-74 depend from claim 71 and generally correspond with claims new 68-70.

Rejection Under 35 U.S.C. § 103

Claims 55-57 and 67 were rejected under 35 U.S.C. § 103(a) as obvious over U.S. Published Application No. 2003/0082148 to Ludwig, *et al.* ("Ludwig") in view of U.S.

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Patent No. 5,916,554 to Dionne, *et al.* ("Dionne"). Applicants respectfully traverse this rejection as applied to the amended claims.

The Legal Standard

When applying 35 U.S.C. § 103, the following tenets of patent law must be adhered to:

- (a) determining the scope and contents of the prior art;
- (b) ascertaining the differences between the prior art and the claims at issue;
- (c) resolving the level of ordinary skill in the pertinent art; and
- (d) evaluating evidence of secondary considerations.

Graham v. John Deere, 383 US 1, 17-18, 148 U.S.P.Q. 459, 467 (1966). These four factors are traditionally referred to as the "Graham factors". The Graham factors were affirmed by the U.S. Supreme Court in *KSR International Co. v. Teleflex, Inc.*, 127 S. Ct. 1727, 82 U.S.P.Q.2d 1385 (2007).

Evidence of secondary considerations to be considered in an analysis under 35 U.S.C. § 103 include commercial success, long felt but unresolved needs, failure of others, etc. M.P.E.P. § 2145, *citing Graham*, 383 U.S. at 17, 148 U.S.P.Q. at 467. Evidence may also include evidence that the claimed invention yields unexpectedly improved properties or that the claimed invention possesses unexpected properties. M.P.E.P. § 2145, *citing In re Dillon*, 919 F.2d 688, 692-93, 16 U.S.P.Q.2d 1897, 1901 (Fed. Cir. 1990).

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Analysis

1. Determining the scope and contents of the prior art

Ludwig

Ludwig discloses devices for recruiting endothelial cells circulating in the blood stream of a subject, to adhere to a surface of an implant that is in contact with blood, referred to as a “blood contacting surface”. *See Ludwig, Abstract, para. [0039] and para. [0041].* Ludwig is directed at retaining endothelial cells on the surfaces of implants to increase their compatibility with blood and thereby make these devices anti-thrombogenic. *See Ludwig, para. [0004] and [0005].*

In one embodiment, recruiting the target cells to the surface involves magnetically attracting the target cells so that they adhere to the surface. *See Ludwig, para. [0060] - [0071].* In this embodiment, compounds within the surface of the implant may be modified to include a magnetic component, and the target cells may also be modified to include a magnetic component, for example, by attaching the cells to nano- or microparticles containing ferromagnetic particles. *See Ludwig, para. [0064] and para. [0107].*

In another embodiment, recruiting the target cells to adhere to the surface involves introducing onto the surface ligands that have an affinity for the target cells. *See Ludwig, para. [0012] and para. [0072]-[0078].* The recruitment of target cells to the surface includes the step of providing a blood contacting surface positioned in the blood stream of a subject. *Ludwig, para. [0011].*

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Dionne

Dionne discloses a biocompatible flexible pouch for use in implanting cell bodies that produce a therapeutic agent. Dionne, Abstract. The cells remain in the pouch and are removed from the patient when they are no longer useful by removing the pouch. See Dionne, col. 1, lines 47-52 and col. 2, lines 27-38.

2. Differences between the claims and the prior art

Ludwig does not disclose nor make obvious an implant as claimed. For example, Ludwig does not disclose nor make obvious:

- (i) including in the implant an external porous housing having pores of a size sufficient to allow movement into the implant of the progenitor cells to be recruited, or
- (ii) including in the implant a plurality of particles having a diameter ranging from 10 nanometers to 10 microns, where the particles also contain one or more cytokines.

Further, even if Ludwig was combined with Dionne, as proposed by the Examiner, the combination would not make up for Ludwig's deficiencies.

a. Ludwig does not disclose a drug delivery device, let alone a device comprising a plurality of particles having a diameter ranging from 10 nanometers to 10 microns

Ludwig discloses that proteins, such as growth factors, may be loaded into the polymer matrix such as a hydrogel, which **coats** the blood contacting surface. Ludwig, para. [0109] (emphasis added). This disclosure of a growth factor-containing hydrogel coating layer is not a disclosure of a **drug delivery** device. This is because Ludwig defines a coating layer as a layer or mixture which may contain specific ligand binding molecules or magnetic particles which will be functionally **attached, immobilized,**

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bound or adsorbed onto the blood contacting surface. Ludwig, para. [0053] (emphasis added). By contrast, one of ordinary skill in the art would understand delivery of a growth factor to mean the growth factor leaves the location at which it is found and is transported to a spatially distinct location. This is not contemplated in Ludwig and is not desired by Ludwig. Ludwig attaches the growth factors to the surface of its device to recruit endothelial cells circulating in the blood stream of a subject to adhere to the surface of the prosthesis. Ludwig, paras. [0053], [0093] and [0101]. Ludwig is directed at endothelializing the surface, and therefore requires the attachment of the ligands to the surface.

Ludwig's disclosure with respect to nano- or microparticles (Ludwig, para. [0064]) or beads (Ludwig, para. [0162]) to which the Examiner cites, is only relevant the embodiment of magnetically attracting cells of interest to the surface of the prosthesis. For example, Ludwig discloses that para- or ferromagnetic particles may be enclosed within a polymer matrix of micro- and nanoparticles, and then attached to the cell of interest. The cells are thereby magnetically labeled, so that they can attach to a magnetized prosthetic device.

Neither of these embodiments serves as a drug delivery device that releases cytokines. Further Ludwig does not disclose a device that is designed to release cytokines from small (10 nanometers to 10 microns) particles.

b. There is no motivation to modify the disclosure in Ludwig to include a drug delivery device as required by the claims

As noted above, Ludwig discloses prosthetic devices that are modified to contain a layer or mixture that includes ligand binding molecules attached to the blood contacting

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surface. Thus, Ludwig requires for there to be a connection between the blood contacting surface and the ligand. In view of this requirement, there would be no motivation to modify the device in Ludwig to release the ligand from the surface of the device.

Further, Ludwig teaches away from such a modification since Ludwig requires the attachment of the ligand to the blood contacting surface to achieve its purpose of recruiting and adhering cells to endothelialize its blood contacting surface.

Modifying the devices in Ludwig to release the ligands to a spatially distinct location would change the principle of operation of the device in Ludwig and prevent it from achieving its purpose. Such a modification is impermissible under 35 U.S.C. § 103(a). *See MPEP § 2143.01(V) and (VI).*

c. Ludwig does not disclose nor desire an external porous housing in their devices.

Although the Examiner acknowledges that Ludwig does not disclose an external porous housing, the Examiner relies on Dionne for providing this disclosure. Office Action mailed July 30, 2010, page 4, para. 4. However, it is unclear how Dionne makes up for the absence of “an external porous housing having pores of a size sufficient to allow movement into the implant of the progenitor cells to be recruited”.

Dionne provides a flexible pouch that allows for the retrieval of the pouch (containing the cells placed within the pouch before/during implantation), after implantation of the pouch. *See* Dionne, col. 6, lines 32-36. According to Dionne, the ability to retrieve the cells is a significant advantage over the prior art. The fact that cells, which were included in the pouch initially, can later be retrieved by removing the pouch

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demonstrates that the cells do not leave the pouch. Thus for embodiments utilizing a ‘porous’ pouch, the porosity is such that **cells cannot pass through the pouch**.

Thus, even if one were to modify the device in Ludwig to contain a pouch as disclosed in Dionne, the pouch would not be an external porous housing having pores of a size sufficient to allow movement into the implant of the progenitor cells to be recruited, as required by the claims.

d. There is no motivation to modify the disclosure in Ludwig to include an external porous housing

Ludwig is concerned with modifying prosthetic devices containing a surface in contact with blood. In one embodiment, these surfaces are modified to contain ligands that recruit endothelial cells, when the device is positioned in the blood stream of a subject. See Ludwig, para. [0011]. Based on the structure and purpose of the device disclosed by Ludwig, there is no reason why one of ordinary skill in the art would go to the trouble of adding a porous housing to the device.

The Examiner’s attention is drawn to the U.S. Patent Office’s updated obviousness guidelines, *Examination Guidelines Update: Developments in the Obviousness Inquiry After KSR v. Teleflex*, Fed. Reg. 75 (169): 53643-53660 (Sept. 1, 2010) (“the 2010 Obviousness Guidelines”). The 2010 Obviousness Guidelines note that one situation in which it is important to identify a reason to combine known elements is when the combination requires a greater expenditure of time, effort or resources than the prior art teachings. Fed. Reg. 75 (169) at page 53646, middle col. Adding an external porous housing to the devices in Ludwig is not only useless to the devices in Ludwig, but it would require more time, effort and resources than Ludwig teaches.

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Ludwig places its devices directly in the path of blood flow to recruit the desired cells. Ludwig, para. [0011]. Thus, there is no reason why one of ordinary skill in the art would add an external porous housing in the devices disclosed in Ludwig since it would prevent the device from being in direct contact with the blood flow. *See* Fed. Reg. 75 (169) at page 53647, left col., which discusses this reasoning as applied to *In re Omeprazole*, 536 F.3d 1361 (Fed Cir. 2008).

According to the Examiner, it would have been obvious to try the nylon mesh pouch disclosed in Dionne for implanting the graft prosthesis of Ludwig. Applicants note that in order to use the mesh as an implanting device, the nylon mesh is tethered to a tissue pedicle and the opening of the pouch is such that it is secured to the tissue pedicle. *See* Dionne, col. 4, lines 43-58. Further, the mesh is enclosed at one end; this feature would be necessary in order to use the mesh as an implantation tool. *See* Dionne, Figure 1.

Ludwig requires placing at least one surface of its device in the path of bloodflow to achieve the desired cell recruitment. Therefore, one of ordinary skill in the art would not use the mesh in Dionne to surround Ludwig's prosthetic device as contemplated by the Examiner, since the mesh would interfere the contact between the blood and the surface of the device. Thus, freely flowing blood would not be in direct contact with the surface of Ludwig's device, and this obstruction would reduce the recruitment of cells to the surface of the device. References cannot be combined where the references teach away from their combination. *See* MPEP § 2145(X)(D)(2).

For at least the reasons discussed above, the claims as amended are non-obvious over the combination of Ludwig and Dionne.

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New Claims 71-74

New claims 71-74 are non-obvious over the combination of Ludwig and Dionne for at least the following reasons. New independent claim 71 defines a plurality of particles for recruiting progenitor cells to a site in the body of a subject,

wherein the particles having a diameter ranging from 10 nanometers to 10 microns,

wherein the particles comprise one or more cytokines, and

wherein the cytokines are released *in vivo* from the particles in a controlled or sustained manner..

Ludwig does not disclose nor make obvious the claimed plurality of particles

Ludwig is directed at endothelializing the surface, and therefore requires the attachment of ligands to the surface.

Ludwig discloses that proteins, such as growth factors, may be loaded into the polymer matrix such as a hydrogel, which **coats** the blood contacting surface. Ludwig, para. [0109] (emphasis added). This disclosure of a growth factor-containing hydrogel coating layer is not a disclosure of a **drug delivery** device because Ludwig defines a coating layer as a layer or mixture which may contain specific ligand binding molecules or magnetic particles which will be functionally **attached, immobilized, bound or adsorbed** onto the blood contacting surface. Ludwig, para. [0053] (emphasis added). By contrast, one of ordinary skill in the art would understand delivery of a growth factor to mean the growth factor leaves the location at which it is found and is transported to a spatially distinct location.

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Ludwig's disclosure with respect to nano- or microparticles (Ludwig, para. [0064]) or beads (Ludwig, para. [0162]) to which the Examiner cites, is only relevant the embodiment of magnetically attracting cells of interest to the surface of the prosthesis.

Neither of these embodiments releases cytokines. Further Ludwig does not disclose releasing cytokines from small (10 nanometers to 10 microns) particles.

Dionne does not cure the defects of Ludwig. Dionne discloses a biocompatible flexible pouch for use in implanting cell bodies that produce a therapeutic agent. Dionne, Abstract. Dionne does not disclose microparticles, let alone particles that release cytokines.

Therefore new claims 71-74 are non-obvious in view of Ludwig, alone or in combination with Dionne.

Allowance of claims 55-57, and 67-74, as amended, is respectfully solicited.

Respectfully submitted,

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